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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/345,815	06/30/99	UCKUN	F 957.001US1

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EXAMINER	
ROBINSON,P	
ART UNIT	**PAPER NUMBER**
1653	9

DATE MAILED: 06/08/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/345,815	Applicant(s) UCKUN, FATIH M.	
	Examiner Patricia A. Robinson	Art Unit 1653	

-- The MAILING DATE of this communication appears on th cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,5,10-13 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,5,10-13 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

Applicant's response, paper no. 8, filed 5/1/2000 is acknowledged.

The specification has been amended by deleting Figures 1-4 and replacing them with new Figures 1-4.

The claims have been amended in the following manner: (1) claims 1-3, 6-9 and 14 are cancelled; (2) claims 4-5, 10-13 are amended; and (3) claim 15 is added.

In view of the amendments indicated in the preceding paragraph, the following grounds of rejection are, or remain, applicable to pending claims 4-5, 10-13 and 15. All other grounds of rejection and objection are hereby withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a), which forms the basis for all obviousness rejections, set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

Applicant's arguments to the above rejection, filed in Paper No. 8, page 4 are: (1) the standard for anticipation is strict identity and that in order to anticipate a claim a

single prior art source must contain all its elements; and (2) that Myers et al. fails to meet this standard because the reference does not teach or suggest a method of inhibiting c-jun activation, nor the use of a quinazoline to achieve the desired inhibition of c-jun activation.

Applicant's arguments filed in Paper No. 8, 5/1/2000 have been fully considered but they are not persuasive because the inhibition of c-jun as disclosed in Applicant's specification is accomplished **only** indirectly by inhibiting JAK-3. JAK-3 is a species of tyrosine kinases and Myers et al. teaches "fine-tuning for selectivity vs. other tyrosine kinases is possible using a quinazoline as a template." (See page 420). Moreover, Myers et al. teaches a **method** of using these inhibitory compounds in treatment of protein tyrosine-kinase regulated diseases. (See page 417). Therefore, JAK-3 would be a candidate for inhibition and would prohibit the subsequent series of events necessary to culminate in the final outcome of the c-jun regulated biochemical signal transduction cascade that affect proliferation and survival of B-lymphoid cells. Thus, it one of ordinary skill in the art would recognize the nexus that by inhibiting an upstream step in a process cascade, all downstream activity would also be inhibited. The reference teaches all of claim 10 and 15 and the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Therefore, the rejection of claim 10, as being obvious in view of the Myers et al. reference, is maintained and claim 15 is rejected.

Claims 4-5, 11-13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karin, et al, "AP-1 Function and Regulation", Cell Biology, 9:240-246, in view of Riedy et al., "Genomic Sequence, Organization, and Chromosomal Localization of Human JAK-3", Genomics 37: 57-61, Rosette and Karin, "Ultraviolet Light and Osmotic Stress: Activation of the JNK Cascade Through Multiple Growth Factors and Cytokine Receptors", Science, 274:1194-1197; and Chae, et al "Role of Tyrosine Phosphorylation in Radiation-induced Activation of c-jun Protooncogene in Human Lymphohematopoietic Precursor Cells", Cancer Research 53:447-451.

Applicant claims a method of inhibiting c-jun activation by contacting the cells with a substance that inhibits the activity of Janus family kinase 3 (JAK-3).

In Karin et al. c-jun and c-fos are disclosed as both belonging to the same family of transcription factors. Karin et al. states further that very stable heterodimer structures are formed between c-jun and c-fos and that the two factors are simultaneously over expressed during osteosarcoma formation. Indicating an in vivo cooperation between c-jun and c-fos. Karin et al. goes still further to teach that c-jun is expressed in response to UV radiation and cytokine exposure, and that exposure activates the p38 and Jun amino terminal kinases (JNKs). See pages 240-242. Karin et al. teaches the fact that c-jun is required for fibroblast proliferation, and that the level of c-jun gene expressed in a cell is shown to increase in response to stimuli, including cytokines and UV radiation. Id. In addition, activating proteins (AP-1), including c-jun and c-fos, play a role in cell apoptosis as evidenced in the increased expression of c-jun and c-fos in response to various stresses, including UV irradiation. See pages 243-244. Karin et al. discloses

that c-jun also plays a role in ceramide-induced apoptosis, where JNK activation is essential for induction of apoptosis due to JNK's ability to induce c-jun transcription. Id. Finally, Karin et al. teaches that inhibition of AP-1, i.e. c-jun, blocks apoptosis and that AP-1 may play a role in providing a protective function in response to stresses such as UV irradiation in fibroblasts. Karin et al. does not teach the use of a specific inhibiting compound of JAK-3 as a means of inhibiting c-jun activation, nor does it teach the B-lymphocyte application in particular, merely fibroblasts in general.

Riedy et al., "Genomic Sequence, Organization, and Chromosomal Localization of Human JAK-3", Genomics 37: 57-61 teaches the activation of JAK-3 by cytokines in B-cells. See pages 58-59. While, Rosette and Karin teach the activation of tyrosine kinases and induced expression of cytokines by ultraviolet irradiation. See pages 1194-1195. In addition, Rosette and Karin also teach tyrosine kinase inhibitors block c-jun induction by ultraviolet light. See page 1194.

Chae, et al. teaches protein tyrosine kinase activation as preceding and mandating radiation-induced activation of c-jun protooncogene expression B-lymphocyte cells. See Abstract and page 447.

It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to utilize a Janus kinase inhibitor to prevent the activation of the c-jun protooncogene in response to cellular stress. The literature demonstrates that JAK activation, and in particular JAK-3, precedes and has regulatory power over the induction of c-jun protooncogene expression. Thus, it would have been

prima facie obvious that by inhibiting JAK-3, one could mediate the expression of c-jun downstream.

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over over Karin, et al, "AP-1 Function and Regulation", Cell Biology, 9:240-246, in view of Riedy et al., "Genomic Sequence, Organization, and Chromosomal Localization of Human JAK-3", Genomics 37: 57-61, Rosette and Karin, "Ultraviolet Light and Osmotic Stress: Activation of the JNK Cascade Through Multiple Growth Factors and Cytokine Receptors", Science, 274:1194-1197; and Chae, et al "Role of Tyrosine Phosphorylation in Radiation-induced Activation of c-jun Protooncogene in Human Lymphohematopoietic Precursor Cells", Cancer Research 53:447-451 as applied to claims 4-5, 11-13 and 15 above, and further in view of Myers et al., Narla et al. and Leonard et al., as directed to the species 4-(3' –bromo-4' –hydroxylphenyl)-amino-6,7-dimethoxyquinazoline and 4-(4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline.

Karin et al is applied here as discussed in the preceding paragraphs in the rejection of claims 4-5, 11-13 and 15. Insofar as Karin et al. did not indicate use of a compound that inhibits JAK-3 specifically, it would have been obvious to one of ordinary skill in the art to have modified the teachings in Karin et al. because utilizing a compound known to inhibit JAK-3 would clarify the exact role JAK-3 plays in the overall cascade by elucidating what downstream factors are being regulated by JAK-3. Thus, yielding a greater understanding of the entire process necessary in formulating methods of inhibiting cell apoptosis.

Myers et al. discloses the results from a SAR study examining the inhibitory effect of quinazoline-based compounds on several species of tyrosine kinases. (See abstract and page 417). In particular, Myers et al. discloses a base compound, 6,7-dimethoxyquinazolinone, and tests a myriad of different moieties at different positions. (See page 418). Myers et al. discloses a 4-hydroxyphenyl moiety with the 6,7-dimethoxyquinazolinone backbone and in addition teaches the importance of an amine linker for enhanced inhibitory effect. (See page 418-419). Finally, Myers et al. states, "The accompanying paper demonstrates that fine-tuning for selectivity vs. other tyrosine kinases is possible using a quinazoline as a template." (See page 420). Thus, it would have been clearly anticipated to take the teachings of Myers et al. and further fine tune the compound and test its effectiveness against other members of the genus of tyrosine kinases. Disclosure of a species will anticipate a claim to a genus and further, a reference that clearly names the claimed species anticipates the claim no matter how many other species are named in that reference. The purpose of the "fine tuning" was to identify additional species belonging in the genus, thus by carrying out the teachings and identifying the additional species, the claimed species are *prima facie* obvious. Therefore the use of quinazolines to inhibit tyrosine kinases, including JAK-3, is taught in Myers et al. (See pages 417-418).

In addition, Narla et al. teaches the novel quinazoline derivative 4-(3' –bromo-4' –hydroxylphenyl)-amino-6,7-dimethoxyquinazoline and 4-(4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline as an inhibitor of the EGF-R tyrosine kinase. (See page 1405, footnote 2 and 1409, col. 2, first paragraph). Moreover, Narla et al. teaches the fact that

the cytotoxicity of the quinazoline failed to cause any detectable cytotoxicity to glioblastoma cells and postulated that the cytotoxicity the quinazoline can not be explained by its tyrosine kinase inhibition alone, but another member of the biochemical signal transduction cascade is also being inhibited by the quinazoline. (See page 1409-1410). Finally, Narla et al. teaches identifying the additional molecular target (e.g., other biological agents, different cytokines, etc.) in the cascade that is being inhibited by the quinazoline. (See page 1414).

Lastly, Leonard teaches that identification of compounds that inhibit JAK-Stat signaling pathway would be useful in treating disorders controlled or impacted by this pathway. (See page 16, lines 29-34). Leonard also teaches further testing of drugs that inhibit proliferation of affected cells in order to determine which disorders they would be used to treat. (See page 16, lines 34-36). Finally, Leonard teaches the fact that when a final undesirable outcome is created via a pathway, inhibiting that pathway anywhere in the cascade will inhibit its culminating in creating the undesirable outcome. (See page 17, lines 1-6).

Applicant's arguments to the above rejections under 35 U.S.C. 103(a), filed in Paper No. 8, pages 4-6 are, in summary, that a *prima facie* case of obviousness was not established with the references cited.

In response to all of Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413,

208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that Karin et al. does not teach any quinazoline compounds nor the usefullness of quinazoline compounds for inhibiting c-jun activation. However, Chae et al. teaches the nexus within the biochemical cascade between upstream tyrosine kinase activation and downstream c-jun. Chae et al. goes farther and specifically teaches that inhibition of the upstream tyrosine kinase will block the downstream activation of c-jun. Finally, as disclosed in Applicant's specification at page 9, lines 20-28 inhibitors of JAK-3 are easily identifiable in the art. Thus, it would have been obvious to one of ordinary skill in the art to take the teachings of Karin et al. and incorporate the teachings of Chae et al. and Myers et al. (in addition to the admitted knowledge in the art) which references when combined teach all of the claimed invention.

Therefore, the rejection of claims 4-5,10-13 and 15 is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Robinson whose telephone number is 703-305-0096. The examiner can normally be reached on 8:00 - 4:30 Monday - Friday, off alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 703-308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

PAR
June 2, 2000

CHRISTOPHER S. F. LOW
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